European Society of Hypertension

Scientific Newsletter
Update on Hypertension Management

2014, 15, nr. 59

EVALUATION OF EARLY TARGET DAMAGE DURING ANTIHYPERTENSIVE TREATMENT

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Introduction

Hypertension-induced mortality and morbidity is produced through the impact on the heart, the central nervous system, the vessels and the kidney. Evaluation of early target organ damage (TOD) in these organs is an important step in a risk stratification strategy to reduce cardiovascular and renal damage. The ESH-ESC Guidelines published in 2007 (1) stated that "Further emphasis has been given to identification of target organ damage, since hypertension-related subclinical alterations in several organs indicate progression in the cardiovascular disease continuum which markedly increases the risk beyond that caused by the simple presence of risk factors" The reappraisal of the ESH of 2009 (2) and thereafter the ESH-ESC Guidelines 2013 (3), encouraged the convenience of repeating TOD assessment during the follow-up.

Risk stratification

Despite the difficulties to quantify how much the risk increases with the presence of one or more of the TOD, the presence of TOD upgrade the risk category for a given BP value and other CV risk factors (3). There is a consensus that if TOD is present in different organs they seem to have additive prognostic value implying increased cardiovascular risk. Subjects with low or moderate risk are those that potentially may upgrade the risk after assessing TOD. A panel of TOD was included in the 2013 guidelines (Table 1), although some of them, such as the ankle/brachial index or estimated glomerular filtration rate <60ml/min/1.73 m2, indicates advanced organ damage. Others are not available for routine use. Based on availability, cost and clinical significance, left ventricular mass assessment, urinary albumin excretion and glomerular filtration rate are the minimal recommended.

Table1 - Predictive value, availability, reproducibility and cost-effectiveness of some markers of organ damage (3)

Marker	Cardiovascular predictive value	Availability	Reproducibility	Cost-effectiveness
Electrocardiography	+++	++++	++++	++++
Echocardiography, plus Doppler	++++	+++	+++	+++
Estimated glomerular filtration rate	+++	++++	++++	++++
Microalbuminuria	+++	++++	++	++++
Carotid intima–media thickness and plaque	+++	+++	+++	+++
Arterial stiffness (pulse wave velocity)	+++	++	+++	+++
Ankle–brachial index	+++	+++	+++	+++
Fundoscopy	+++	++++	++	+++
Additional measurements				
Coronary calcium score	++	+	+++	+
Endothelial dysfunction	++	+	+	+
Cerebral lacunae/white matter lesions	++	+	+++	+
Cardiac magnetic resonance	++	+	+++	++

Scores are from + to ++ + +.

Follow-up

Several studies have shown that the regression of asymptomatic TOD occurring during treatment reflects the treatment-induced reduction of morbid and fatal CV events, thereby offering valuable information on whether patients are more or less effectively protected by the treatment strategies adopted.
The changes in electrocardiographically or echocardiographically left ventricular hypertrophy (LVH) induced by treatment reflect the effects on cardiovascular events, thereby offering valuable information on whether patients are more or less effectively protected by the adopted treatment strategy. In fact, several studies have demonstrated a reduction in the risk of mortality or in the incidence of stroke, coronary events, congestive heart failure among hypertensives who reduce ECG voltage or strain or echo left ventricular mass (4). In the echocardiographic sub-study of the LIFE trial there was decrease of about 20% of the primary end point for one standard deviation of reduction of LV mass (i.e. 25 g/m2). Additionally, left atrial dimension paralleled the changes in LV mass, suggesting the possible mechanism by which changes in LVH are associated with changing risk of developing atrial fibrillation. Moreover, changes in LV geometry during treatment may have additional prognostic significance in patients with and without LVH (5,6), the most severe situation being persistence or development of concentric hypertrophy.
Some evidence suggests that this is the case also for treatment-induced changes in urinary protein excretion. In fact, a reduction in total mortality and cardiovascular mortality has been observed when a significant urinary albumin excretion reduction is achieved (7), however some inconsistent results have been recently reported (ref).
The problem remains open for treatment-induced vascular changes since the changes overtime are minimal or no studies have addressed the issue. It is also possible that in very high risk patients, such as in those who already suffered a cardiovascular event, the reduction of LVH and/or of proteinuria may not be associated with reduced incidence of future cardiovascular events (8), because the disease is so advanced that the risk is no longer linked to markers of initial organ damage.
Despite the great bulk of information available demonstrating an association between regression of TOD during antihypertensive treatment and decreased mortality and cardiovascular and renal morbidity, some key questions for the clinically use of TOD remain unmet. Among them, the marker(s) alone or in combinationto be used, the most appropriate timing to repeat them and whether or not changes in one organ can be assumed to occur in the other organs. Finally, a question to consider is if some of these TOD should be targeted during the antihypertensive treatment beyond the BP reduction.
In the meantime awaiting solid information to support clear recommendations, it is interesting to look on selection and timing of the TOD

measurements for the follow-up during antihypertensive treatment. The most important factors are availability, cost, sensitivity for detecting changes, time necessary for observing the changes and finally the evidence for prognostic value of the changes. The current knowledge about these factors is summarized in the Table 2.

Availability

Availability of a marker is critical considering the high prevalence of hypertension. The majority of hypertensive patients are managed by primary care physicians with different levels of resources and skills in the interpretation of the tests. In Europe, ECG, eGFR and urinary albumin excretion, which are considered the minimum required to stratify cardiovascular risk using the ESH-ESC Guidelines, can also be recommended for follow-up. Assessment of echocardiographic left ventricular mass and ultrasound carotid wall thickness are only available at the specialist level. Although the availability of PWV is increasing, it is still restricted to hypertension specialists.

Cost

Management of hypertension represents an important burden for health care due to the high prevalence of the disease and the necessity to maintain treatment and visits for several years. In addition to that, the cost of additional periodic assessments of TOD must be considered. Besides having the highest availability, ECG, eGFR and urinary albumin excretion are the cheapest markers of TOD. Echocardiographic assessments of the heart and the carotid arteries require an initial investment for buying the equipment and are also time-consuming and therefore rather expensive. Assessment of PWV does not require expensive equipment and is becoming easier and faster to perform making it cheaper, thus resulting in an intermediate cost.

Sensitivity to detect changes

This is a crucial factor since changes during treatment should be measurable and reliable. Voltage and strain changes in the ECG are easy to measure and are not operator-dependent but require rather large changes due to considerable day to day variation. Echocardiography that has a higher sensitivity requires a change of at least 10% or better of 20%, which approximately equals 1SD, to be classified as a true change. Since quantitative urinary albumin excretion measure has a high intra-individual variability and can be affected by several factors a true change require a regression or an increment of more than 50% of the initial value, although having two measurements in different days and calculating average can help to reduce the concern about variability. For the intima-media thickness of the carotid wall, the changes are rather small making difficult to quantify changes during treatment. Regarding pulse wave velocity, BP changes itself modify the values making it difficult to get reliable information.

Timing of detectable changes

The time necessary to observe changes is another key issue. Changes in ECG and carotid wall thickness requires more than one year, echocardiographic measurement of left ventricular mass often requires more than 6 months. In contrast, urinary albumin excretion changes fast, within weeks to a few months.

Prognostic value of TOD changes

That changes in left ventricular mass, assessed by ECG or echocardiography, as well as changes in urinary albumin excretion have prognostic implications demonstrated in a large number of studies commented above. The prognostic value of changes in carotid wall thickness has not been conclusive and no clear evidence exists for the prognostic value of changes in pulse wave velocity. The regression or improvement of more that one organ damage, i.e. LVH plus proteinuria (9) or LVH plus GFR (10), seems to confer an additional benefit in terms of better prognosis.

Table2 - Sensitivity to detect treatment-induced changes, time to change and prognostic value of change by markers of asymptomatic TOD (3)

Marker of organ damage	Sensitivity for changes	Time to change	Prognostic value of changes
LVH/ECG	Low	Moderate (>6 months)	Yes
LVH/echo	Moderate	Moderate (>6 months)	Yes
LVH/cardiac magnetic resonance	High	Moderate (>6 months)	No data
eGFR	Moderate	Very slow (years)	No data
Urinary protein excretion	High	Fast (weeks–months)	Moderate
Carotid wall thickness	Very low	Slow (>12 months)	No
Pulse wave velocity	High	Fast (weeks–months)	Limited data
Ankle/ brachial index	Low	No data	No data

ECG = electrocardiogram; echo = echocardiogram; eGFR = estimated glomerular filtration rate; LVH = left ventricular hypertrophy; OD = organ damage.

Conclusion

Based on these considerations ESH/ESC guidelines 2013 concludes that measuring serum creatinine, urine albumin excretion and electrocardiographic left ventricular mass in patients with hypertension is a class I recommendation with an evidence level B. However, the new guidelines also states that measuring echocardiographic left ventricular mass, ultrasonic carotid wall thickness, aortic PWV and ankle-brachial index is a class IIa recommendation (should be considered) with an evidence level B.

Recognizing the need for more evidence regarding which combination of markers to measure, at what time points, in which patients, and with which consequence, efforts should be performed to gain grounded information for a better clinical use of TOD during antihypertensive treatment.

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